

Review

High-frequency ECG

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Introduction

The standard ECG is by convention limited to 0.05-150 Hz, but higher frequencies are also present in the ECG signal [Golden *et al.*, 1973]. With high-resolution technology, it is possible to record and analyze these higher frequencies. The highest amplitudes of the high-frequency components are found within the QRS complex (figure 1). In past years, the term “high frequency”, “high fidelity”, and “wideband electrocardiography” have been used by several investigators to refer to the process of recording ECGs with an extended bandwidth of up to 1000 Hz. Several investigators have tried to analyze HF-QRS with the hope that additional features seen in the QRS complex would provide information enhancing the diagnostic value of the ECG.

The development of computerized ECG-recording devices that made it possible to record ECG signals with high resolution in both time and amplitude, as well as better possibilities to store and process the signals digitally, offered new methods for analysis. Different techniques to extract the HF-QRS have been described. Several bandwidths and filter types have been applied for the extraction as well as different signal-averaging techniques for noise reduction. There is no standard method for acquiring and quantifying HF-QRS.

The physiological mechanisms underlying HF-QRS are still not fully understood. One theory is that HF-QRS are related to the conduction velocity and the fragmentation of the depolarization wave in the myocardium. In a three-dimensional model of the ventricles with a fractal conduction system it was shown that high numbers of splitting branches are associated with HF-QRS. In this experiment, it was also shown that the changes seen in HF-QRS in patients with myocardial ischemia might be due to the slowing of the conduction velocity in the region of ischemia [Abboud *et al.*, 1991]. This mechanism has been tested by Watanabe *et al.* [Watanabe *et al.*, 1998] by infusing sodium channel blockers into the left

anterior descending artery in dogs. In their study, 60 unipolar ECGs were recorded from the entire ventricular surface and were signal-averaged and filtered in the 30-250 Hz frequency range. The results showed that the decrease noted in the HF-QRS correlated linearly with the local conduction delay. The results suggest that HF-QRS is a potent indicator of disturbed local conduction. An alternative theory is that HF-QRS reflect the shape of the original electrocardiographic signal. Bennhagen et al [Bennhagen *et al.*, 2001] showed that root mean square (RMS) voltage values of the depolarization signal correlate poorly with the signal amplitude but highly with the first and second derivatives, i.e. the velocity and the acceleration of the signal. It has also been suggested that the autonomic nervous system affects HF-QRS. For example, sitting up causes significant changes in HF-QRS in some leads compared to the supine position [Douglas *et al.*, 2006]. Unpublished results indicate that familial dysautonomic patients (both vagal and sympathetic degeneration) have very little Reduced Amplitude Zones (RAZ) formation (see below, “Quantification of HF-QRS”). Athletic individuals, especially elite athletes, who have vagally-mediated changes on the conventional ECG (i.e. early repolarization, bradycardia) have increased RAZ formation [Schlegel *et al.*, 2004]. Further electrophysiological studies are needed, however, to better understand the underlying mechanisms of HF-QRS.

Several investigators have studied HF-QRS in different cardiac conditions, including acute myocardial ischemia and myocardial infarction (MI). However, in order for clinicians to confidently use HF-QRS as an adjunct to standard ECG, more knowledge about the characteristics of HF-QRS is needed.

Analysis of HF-QRS

ECG acquisition

In order to be able to extract HF-QRS it is important to use high resolution, both in time and amplitude. In theory, the incoming ECG signals must be sampled (digitized) at least at twice the rate of the highest frequency of interest for the HF signal retention; otherwise the signals will be distorted. This means that if the frequency range of interest is in the 150-250 Hz range, the sampling rate must be at least 500 Hz. In practice a higher sampling rate is required, and in most HF studies the sampling rate has been 1000 Hz or more. Most modern ECG systems have an amplitude resolution of at least 1 μV , which is enough for analysis of HF-QRS.

Noise reduction

The amplitudes of HF-QRS are low (μV) compared to the amplitudes observed in standard ECG (mV). In order to analyze HF-QRS, a low noise level is therefore required. For example, skeletal muscles always contribute noise, which is typically in the high-frequency range. One way of reducing noise from skeletal muscles is to move the electrodes on the legs and arms to more proximal position according to Mason-Likar [Mason & Likar, 1966].

During clinical registration signal averaging is necessary in order to obtain an acceptable signal-to-noise ratio. Therefore the registration sometimes needs to go on for several minutes in order to obtain a large enough number of QRS complexes for averaging. If the ECG morphology is subject to dynamic changes, for example during PTCA, an exponentially (recursively) updated beat average can be used instead, since conventional blockwise averaging is not optimal in such cases.

During the signal averaging the mean amplitude is calculated at each instant of the cardiac cycle from many heart beats. It is important to include values from exactly the same part of the cardiac cycle. To achieve this, a reference point (“fiducial point”) is identified, usually located close to the peak of the R wave. It is equally important that only “normal” beats

are included in the average. Before signal averaging, the predominant beat morphology is selected as a “template beat”. The similarities between the beats are expressed as a cross correlation coefficient [Pahlm & Sörnmo, 1987]. Only beats with a correlation coefficient exceeding 0.97 are usually used for averaging. Signal averaging is continued until the noise is less than a certain level or until a certain number of beats has been included.

The signal averaging process is a well-known source of error during HF-QRS analysis. If the signal averaging is not done with high precision, HF-QRS in the calculated average will be affected. If using a low cross correlation coefficient, beats with different appearances will be lumped together. If the reference point is not reliable, the beats in the average will not be well aligned to one another (“trigger jitter”). These situations result in a reduction of the HF content when averaging.

Extraction of HF-QRS

HF-QRS are extracted from the signal-averaged beats through band-pass filtering. Often, a Butterworth filter is used [Proakis & Monolakis, 1996]. This filter type has a non-linear phase response, which may distort temporal relationships of the various signal components. Linear-phase filtering can be obtained, however, by first filtering the signal forward and then backward. Different studies have used different bandwidths when extracting HF-QRS. Most commonly, however, a frequency range between 150 and 250 Hz has been used.

Quantification of HF-QRS

Several methods have been used for quantification of HF-QRS. One of the most used methods is to calculate RMS voltage values during the entire QRS duration. This method quantifies the average amplitude of the signal and is calculated by:

$$\sqrt{\frac{\sum_{i=1}^n A_i^2}{n}}$$

where n is the number of measurements, and A_i , $i = 1, \dots, n$, are the measured amplitudes. For a correct RMS voltage value it is necessary to correctly identify the beginning and end of the QRS complex. It has been shown that the most correct delineation of the QRS complex is obtained when determining the QRS duration in the standard frequency range.

Another widely used method for quantification of HF-QRS is calculation of RAZs. The RAZ measure is a morphological measure and is defined as an interval between two adjacent local maxima or two adjacent local minima in the HF-QRS, where a local maximum or minimum must have an absolute value higher than the three preceding and three following envelope points. The method was first introduced by Abboud et al [Abboud *et al.*, 1987] in the 1980s. It was discovered that areas with lower amplitude were present in the HF signal in dogs with myocardial ischemia but not in normal dogs. The method has now been further developed by the National Aeronautics and Space Administration (NASA), and 3 different types of RAZs have been identified: Abboud RAZ, Abboud Percent RAZ, and NASA RAZ (most severe) [Schlegel *et al.*, 2004] (figure 2). In addition, a “RAZ score” has been developed, reflecting both the “general RAZ burden” as well as the “RAZ contiguity” in the leads. The general RAZ burden subscore derives from the severest RAZ type that is present in any given lead. In the RAZ contiguity subscore, additional points are added when RAZs are present in leads which are spatially contiguous to one another (the orderly Cabrera sequence is used for limb leads). Other methods for quantification of HF-QRS include the kurtosis (another measure of morphology [Batdorf *et al.*, 2004]), the peak-to-peak amplitude and the integral of the signal.

Basic aspects of HF-QRS

The amplitude of HF-QRS differs among the 12 standard leads. The largest amplitudes are usually found in the anterior-posterior oriented leads V2-V4 and in the inferior-superior oriented leads II, aVF, and III. The lowest amplitudes are found in the left-right oriented leads aVL, I, -aVR, V1, V5, and V6 [Pettersson *et al.*, 2000a]. In the transverse plane, the leads V1 and V6 are located furthest away from the left ventricle, which is a possible explanation for the low amplitudes recorded in these leads. In the frontal plane, however, no leads are located close to the heart, but there is still a large difference in amplitude of HF-QRS between these leads.

The correlation between HF-QRS and the QRS amplitudes in standard ECG is generally low. Other factors than the QRS amplitude in standard ECG thus seem to influence the size of HF-QRS. There is also a large variation in HF-QRS between individuals. During consecutive registrations in the same individual, however, only small variations in HF-QRS are registered [Pettersson *et al.*, 2000a; Batdorf *et al.*, 2004].

HF-QRS in acute myocardial ischemia

Several studies have reported lower HF-QRS amplitudes during acute myocardial ischemia. In a study on dogs, HF-QRS amplitudes were recorded both from epicardial electrodes and from surface electrodes during occlusion of the left anterior descending coronary artery. HF-QRS amplitudes recorded from the epicardium of the left ventricle were significantly reduced during the occlusion, while amplitudes recorded from the non-ischemic right ventricle remained unchanged. Reduced HF-QRS amplitudes were also found on the surface electrodes [Mor-Avi *et al.*, 1987]. Other animal studies have shown similar results [Abboud, 1987; Abboud *et al.*, 1989; Abboud *et al.*, 1990; Mor-Avi & Akselrod, 1990].

In humans, HF-QRS has been recorded during percutaneous transluminal coronary

angioplasty (PTCA) [Pettersson *et al.*, 1998; Pettersson *et al.*, 2000b]. The results from these studies show that balloon-induced ischemia leads to changes in HF-QRS RMS voltages in a majority of the patients. These changes can be observed even when no ST-segment changes are observed in the standard ECG (figure 3). The results indicate that acute myocardial ischemia can be detected with higher sensitivity with analysis of HF-QRS compared to conventional analysis with standard ECG. Analysis of HF-QRS might therefore serve as a complement to standard ECG in the detection of myocardial ischemia. The large inter-individual variation in HF-QRS RMS voltages, however, probably makes such analysis most applicable to monitoring situations when changes from baseline can be identified.

During occlusion of the left anterior descending coronary artery a reduction in HF-QRS is observed in many leads, most commonly in lead V3. During occlusion of other large coronary arteries a reduction in HF-QRS is seen in various leads [Pettersson *et al.*, 2000b]. Thus, HF-QRS may not localize ischemia as well as conventional ECG.

HF-QRS in ischemic heart disease (IHD)

Several studies have compared HF-QRS in patients with old myocardial infarction to HF-QRS in normal subjects. The majority of these studies have shown that HF-QRS amplitudes (RMS voltages) are decreased after myocardial infarction. In the frequency range of 80-300 Hz, HF-QRS amplitudes were significantly decreased in leads V2 and V5 in patients with old anterior myocardial infarction [Goldberger *et al.*, 1981]. In patients with old inferior infarction, HF-QRS amplitudes were decreased in leads II, aVF, and III [Goldberger *et al.*, 1980; Goldberger *et al.*, 1981]. In the frequency range of 150-250 Hz when using the Frank leads (X-, Y-, and Z-leads), decreased amplitudes have also been found in patients with old anterior and/or inferior infarction [Berkalp *et al.*, 1993] and in patients with angiographically documented ischemic heart disease [Seegobin *et al.*, 1995]. However, at least

one study that used three bipolar leads and the >90 Hz frequency range showed increased (rather than decreased) HF-QRS amplitudes in patients with old myocardial infarction [Novak *et al.*, 1994], while another showed that 12-lead RMS voltages in the 150-250 Hz frequency range failed to separate individuals with versus without an old myocardial infarction on the conventional ECG [Ringborn *et al.*, 2001]. Data obtained from studies **analyzing HF-QRS morphology (150-250 Hz)** have generally been less conflicting, and have shown that RAZ counts are significantly increased in individuals with versus without IHD, even when RMS voltage values show no simultaneous differences [Abboud *et al.*, 1986]. In addition, the presence of prior myocardial infarction appears to increase such RAZ counts even further [Schlegel *et al.*, 2004], as does ischemic cardiomyopathy [Schlegel *et al.*, 2005]. Thus, during baseline ECG recordings at rest, changes in HF-QRS morphology may be more consistently sensitive for identifying underlying IHD than changes in HF-QRS amplitude. This finding might be partially explained on the basis of the large inter-individual variations that occur in HF-QRS RMS voltages [Pettersson *et al.*, 2000b; Trägårdh *et al.*, 2004], as noted earlier.

When investigating **serial changes in HF-QRS** in the first year following acute MI, a **statistically significant increase in HF-QRS RMS** voltages from a few days after the MI to follow up during the first year has also been found [Trägårdh *et al.*, 2006b]. The increase, however, was small and not dependent on MI location. Nor were there any differences in HF-QRS RMS voltages when considering the variable of reperfusion treatment versus no treatment. Another study examined HF-QRS (>90 Hz) in patients with different MI locations, and did not find any differences in HF-QRS amplitudes in any lead between patients with anterior, inferior or posterior MI [Novak *et al.*, 1994].

HF-QRS in stress-induced ischemia

Analysis of HF-QRS during exercise testing has been suggested as a complement

to assessment of the ST-segment changes for detection of exercise-induced ischemia. It has been shown that HF-QRS RMS voltages increase during exercise in healthy individuals [Bhargava & Goldberger, 1982]. In a study comparing healthy individuals to patients with ischemic heart disease, it was found that HF-QRS RMS voltages are significantly higher in the healthy population, both during and after exercise [Beker *et al.*, 1996]. One issue with analysis of HF-QRS recorded during exercise is the high noise level generated by skeletal muscle. This issue can be partially addressed through particular focus on the immediate post-exercise recordings. One recent study investigated changes in both HF-QRS morphology and amplitude during adenosine myocardial perfusion imaging stress tests [Rahman *et al.*, 2006]. It was found that when the analysis of resting morphology (RAZ counts) and the dynamic changes in amplitudes (RMS voltages) were combined, HF-QRS was highly sensitive (94 %) and specific (83 %) for detecting reversible perfusion defects, and significantly more sensitive (18 %) than conventional ST-segment analysis.

HF-QRS in left ventricular hypertrophy

Standard ECG is one of the most common methods to detect left ventricular hypertrophy. Several different ECG-based criteria are used clinically. These methods, however, have low sensitivity at high levels of specificity. Studies in rabbits, with and without left ventricular hypertrophy, have shown that HF-QRS correlates well with left ventricular mass [Okin *et al.*, 1992]. In the study, the vector magnitude from orthogonal leads ($\sqrt{X^2 + Y^2 + Z^2}$) in different frequency ranges was studied. High-pass filtering at 44 Hz showed the best correlation between left ventricular mass and HF-QRS ($r = 0.84$). A high correlation between left ventricular mass and HF-QRS was also found among the healthy rabbits alone. However, a study comparing left ventricular mass in normal humans with HF-QRS RMS voltages as well as with standard 12-lead ECG showed that analysis of HF-QRS was no better than analysis of

standard ECG to determine left ventricular mass [Trägårdh et al., 2006a].

HF-QRS in conduction abnormalities

In dogs, HF-QRS are reduced during slow conduction velocity in the heart [Watanabe *et al.*, 1998]. By infusing sodium channel blockers (lidocaine, disopyramide) in the left anterior descending coronary artery at the same time as recording ECGs from the entire ventricular surface, it has been shown that HF-QRS are significantly lower in the areas affected by the sodium channel blockers.

A study comparing patients with left or right bundle branch block with normal subjects and patients with ischemic heart disease showed that patients with intraventricular conduction delay have lower HF-QRS RMS voltages in leads with a positive electrode facing the area of the heart with the conduction delay [Trägårdh et al, in press]. In areas of the heart with normal conduction velocity, the amplitudes of HF-QRS were normal or almost normal. These results suggest that HF-QRS is a potent indicator of disturbed local conduction. Bundle branch blocks also generally lead to substantial RAZ formation [Schlegel *et al.*, 2004], although associated electrode-specific studies of HF-QRS morphology have not yet been performed.

HF-QRS after heart transplantation and heart surgery

Allograft rejection is a major cause of morbidity and mortality in patients who have undergone heart transplant. There is no reliable method for detecting rejection except endomyocardial biopsy. Some studies have investigated whether HF-QRS could be used as a non-invasive marker for rejection [Valentino et al., 1992; Graceffo & O'Rourke, 1996]. The results from the studies have in part showed diverging results, with both an increase and a decrease in HF-QRS RMS voltages at rejection.

In a study on patients after heart surgery, a reduction of HF-QRS correlating with the dysfunction of the heart has been reported [Matsushita *et al.*, 2004]. It is therefore suggested that HF-QRS could be used as a non-invasive marker of myocardial dysfunction after heart surgery. In children who have undergone heart surgery, the change in HF-QRS during aortic clamping has been investigated [Abe *et al.*, 2001]. It was found that the recovery time of HF-QRS significantly correlated with the cardioplegic arrest time during surgery.

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Figure legends

Figure 1. A signal-averaged ECG in the standard frequency range (upper panel) and the same signal-averaged ECG within the 150-250 Hz frequency range (lower panel). Dashed lines indicate the QRS duration.

Figure 2. HF-QRS shown below their respective signal-averaged conventional ECG QRS complexes. Darkened circles in the HF-QRS connote local maxima and minima, whereas arrows (B-D) connote a RAZ. A, High-frequency QRS “normal” complex from lead I that contains no RAZs. B, High-frequency QRS complex from lead aVF that contains an Abboud RAZ on both the upper and lower portion of the signal. The amplitudes of both the secondary local maximum and minimum are insufficient to define an Abboud Percent RAZ because they are less than 30% of the amplitudes of their corresponding primary local maximum and minimum. C, High-frequency QRS complex from lead aVR that contains an Abboud Percent RAZ, which is present because the absolute amplitude of the secondary local maximum that forms the RAZ is at least 30 % of that of the corresponding primary local minimum. D, High-frequency QRS complex from lead V1 that contains a NASA RAZ, because both a secondary local maximum and a minimum are present and both have amplitudes that are at least 30% of the amplitudes of their respective primary local maximum/minimum. From [Schlegel *et al.*, 2004] with permission.

Figure 3. Pre-inflation and inflation signal-averaged ECGs in the standard range (upper panel) and in the high-frequency range (lower panel) in lead V5. Dashed lines indicate the QRS duration. From [Pettersson *et al.*, 2000b] with permission.

Figure 1.

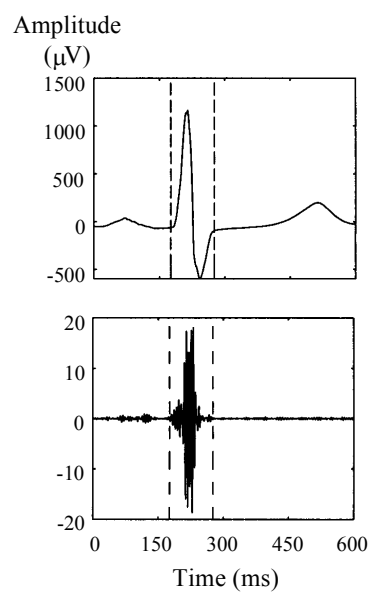


Figure 2.

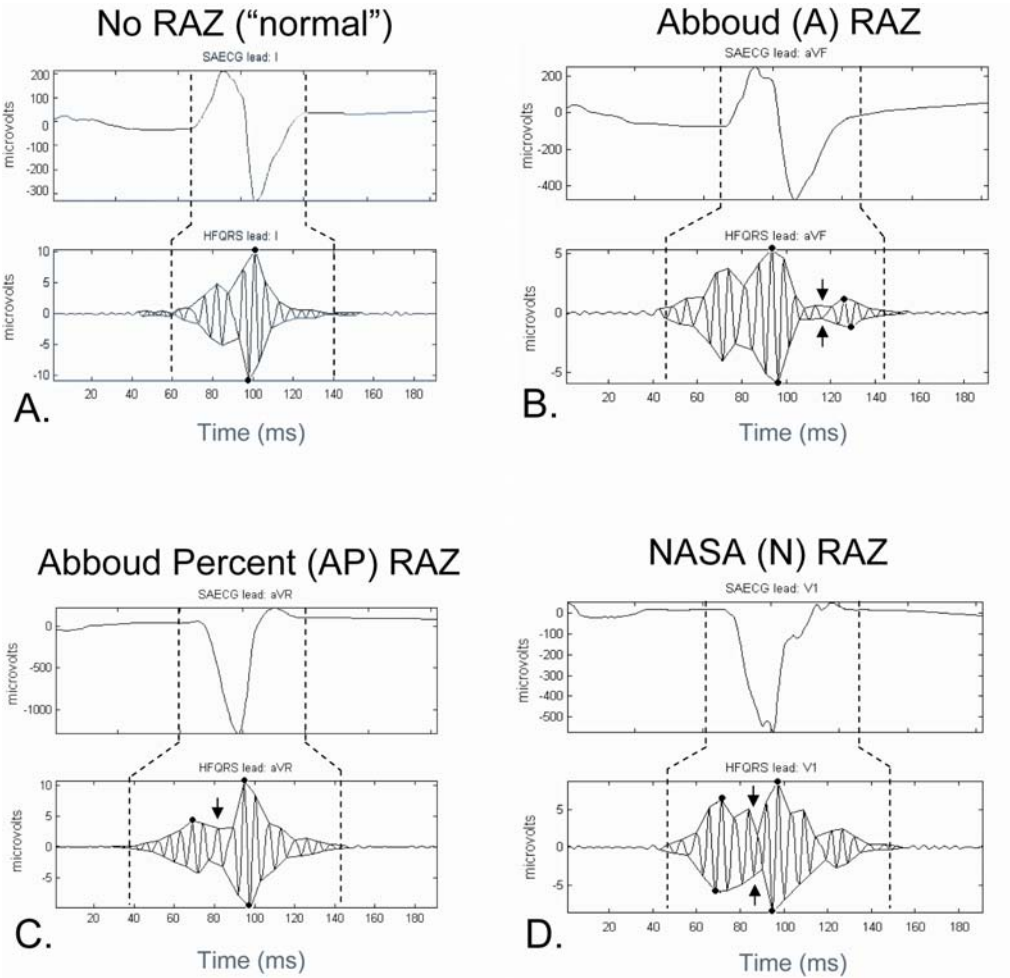


Figure 3.

